Short Communication

Risk of Basal Cell Carcinoma in Relation to Alcohol Intake and Smoking

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Abstract

We prospectively investigated whether alcohol intake and smoking affect the risk of basal cell carcinoma (BCC) in subjects from the United States Radiological Technologists (USRT) cohort study. We evaluated 68,371 radiological technologists certified during 1926–1982 who were free of cancer at the time they answered a first questionnaire (1983–1989) and who completed a second questionnaire (1994–1998). The first questionnaire provided baseline information on numerous risk factors, including smoking and alcohol intake, and the second provided self-reported cancer diagnoses. During 698,190 person-years of follow-up, we identified 1,360 cases of BCC: 1,036 in women and 324 in men. Cox proportional hazards regression indicated that the trend in BCC was significantly associated with increased alcohol intake (*P* for trend = 0.001). Compared with those who reported no alcohol consumption, those who drank <1–2, 3–6, 7–14, and >14 drinks/week had multivariate risks of 1.1 [95% confidence interval (CI), 0.9–1.3], 1.3 (95% CI, 1.1–1.5), 1.4 (95% CI, 1.2–1.7), and 1.0 (95% CI, 0.7–1.6), respectively. We found no clear association between smoking and BCC. This is the second large prospective study to report a significant but nonmonotonic trend in increased risk associated with alcohol consumption.

Introduction

Although basal cell carcinoma (BCC) is the most common cancer among Caucasians (1), few epidemiological studies have examined risk factors for the disease. Of these, most have focused on sunlight exposure and host sun sensitivity characteristics, such as skin pigmentation, eye and hair color, and propensity to tan or burn (2–5). In a recent study, however, Fung *et al.* (6) reported significant positive associations between risk of BCC and total daily alcohol intake when examined prospectively in two large cohorts: the male Health Professionals Follow-up Study and the Nurses Health Study. They noted that previous case–control studies had failed to find any association with alcohol intake (7, 8), but these investigations were characterized by small sample sizes and other limitations. In the absence of other cohort studies of this relationship and to replicate the analysis by Fung *et al.* (6), we examined prospectively (1983–1998) the relationship between BCC and alcohol consumption, as well as cigarette smoking, in the large, nationwide United States Radiological Techologists (USRT) cohort.

Materials and Methods

The USRT Study comprises a cohort of 146,022 radiological technologists who were residing in the United States and certified by the American Registry of Radiological Technologists for at least 2 years between 1926 and 1982 (9, 10). Detailed information on the methods has been provided elsewhere (9). Briefly, we mailed a baseline questionnaire to all cohort members who were located and found to be alive (n = 132,454) during 1983–1989. The questionnaire collected information on height, weight, smoking behavior, alcohol use, and female hormonal factors, as well as work history and other factors. A second questionnaire, administered during 1994–1998, ascertained incident cancers, updated information on the previously evaluated risk factors, and asked about skin pigmentation, hair and eye color, and family medical history. Sixty-eight percent (90,305) responded to the first questionnaire; among living respondents to the initial questionnaire; 83% (70,859) answered the second questionnaire.

Description of Study Population. We restricted this investigation to respondents who answered the baseline questionnaire, were cancer free as of the first questionnaire, and responded to the second questionnaire through August 1998 (n = 68,371). Eligible cases included only first primary BCC cases (*i.e.*, subjects reporting a diagnosis of primary BCC occurring between completion of the two questionnaires). There were no deaths with BCC listed as the underlying or contributory cause of death, based on linkage with the National Death Index.

Pathology reports and other confirmatory medical record information (hereafter the combination of pathology reports and other medical record information is designated as medical records) were requested to validate the self-reported BCCs. Among the 1318 subjects reporting BCC, medical records were obtained for 631 (48%). Of these, medical records validated the BCC diagnosis for 600 subjects (95%). We excluded 32 cases that were incorrectly reported as BCC. An additional 74 subjects with BCC, who had mostly reported other skin cancers, were included in the analysis, bringing the total to 1360 BCC cases.

Data Collection. Age (at questionnaire response), gender, smoking behavior, alcohol intake, education, and work history were obtained from responses to the first questionnaire. The specific question about alcohol requested levels of current consumption: "[h]ow many drinks of alcoholic beverage (beer, wine, or liquor) do you usually have in a typical week?" and

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provided categorical levels, which we grouped as 0, <1–2, 3–6, 7–14, and >14. Thus, the question did not differentiate among types of alcoholic beverages. Smoking information included whether the subject had ever smoked or currently smoked, the daily number of cigarettes smoked, and the duration of smoking.

To compare our results with those of Fung *et al.* (6), we roughly assumed that each drink reported corresponded to ~12 g of alcohol. [Fung *et al.* (6) assigned g/drink depending on the type of drink, which varied from 11 to 14 g/drink.] Applying this conversion factor, our lowest intake level among drinkers, ≤2 drinks/week, roughly corresponded to the lowest intake level reported by Fung *et al.* (0.1–4.9 g/day); our second category, 3–6 drinks/week, to their second category (5.0–14.9 g/day); our third category, 7–14 drinks/week, to their third category (15.0–29.9 g/day); and our highest category, >14 drinks/week, corresponded approximately to their highest category (≥30 g/day).

Because we had not inquired about nonoccupational sunlight exposure in either questionnaire, a proxy measure for mean annual adult residential exposure to sunlight was derived using the estimated annual solar UV radiation assigned to each state (11) in which the subject reported working weighted by the number of years duration of working in that location. In the absence of residential history during childhood and adolescence, a proxy measure for the potential residential sun exposure during childhood was estimated as the annual solar UV radiation assigned to each subject's state of birth. Data on hair, eye, and skin color were derived from the second questionnaire. We did not collect information about individual subjects' tendencies to tan or burn and, therefore, could not adjust for these factors.

Statistical Methods. We used Cox proportional hazards regression analyses to compute relative risks with 95% confidence intervals, using age at diagnosis as the response (*i.e.*, age as the time-scale beginning at completion of the first questionnaire; Ref. 12) and stratifying at baseline for birth cohort in 5-year intervals. Subjects were followed from the first questionnaire until completion of the second questionnaire or the diagnosis of the first cancer, whichever occurred first. Subjects who died without completing the second questionnaire through August 1998 were excluded ($n = 2,378$). Nonrespondents to the second questionnaire ($n = 15,987$) who were presumed alive (based on traces using the National Death Index, Social Security, and other records) were also excluded from the analysis.

Multivariate models included gender (unless stratified by gender), smoking duration, alcohol intake, and established or suspected risk factors for BCC (11), *i.e.,* skin pigmentation, race, and hair color as well as the proxy measures for residential childhood and adult sunlight exposure (quintiles), body mass index (as kg/m^2 in quartiles), education, and the decade a respondent began employment as a radiation technologist. Missing information was analyzed with separate dummy variables. Tests for trend for alcohol and cigarette packs/day smoked were assessed by assigning an ordinal number (as well as by assigning a median value) to each category of intake and modeling this variable as continuous. Otherwise tests for trend were based on continuous variables.

Results

The majority of this study population of cancer-free members of the USRT cohort were female (79%), and ~46% were younger than 35 years when completing the baseline questionnaire (Table 1). Cohort members contributed 698,190 person-years of follow-up. BCC risk was not associated with gender, but rose significantly with age (data not shown). Fair skin, blue and green eyes, and light or red hair were also significantly related to higher risk, as were surrogates for adult and childhood "residential" sunlight exposure (data not shown).

Table 1 Frequency of selected demographic and other characteristics among BCC[a] cases compared with the study population of radiologic technologists in the United States Radiologic Technologists Study cohort[b]

Characteristics	BCC cases ($n = 1,360$)		Study population ($n = 68,371$)	
	n	%	*n*	%
Age at baseline (years)[c]				
<35	424	31.2	31,385	45.9
35–44	445	32.7	23,395	34.2
45–54	302	22.2	9,236	13.5
55–64	133	9.8	3,259	4.8
65+	56	4.1	1,096	1.6
Gender				
F	1,036	76.2	53,807	78.7
M	324	23.8	14,564	21.3
Race				
White	1,335	99.6	65,304	95.5
African-American	1	0.1	1,600	2.3
Asian-American/Pacific Islander	2	0.2	718	1.1
American Indian/Other	2	0.2	749	1.1
Education[d]				
High school (9–12 yrs)	19	1.4	435	0.6
Radiation technology program (2 yrs)	662	48.7	37,139	54.3
1+ years college/graduate school	595	43.8	27,018	39.5
Other/unknown	84	6.2	3,779	5.5
Residence at baseline				
Northeast	261	19.2	17,200	25.2
Southeast	415	30.5	17,095	25.0
Central	342	25.2	21,635	31.6
West	341	25.1	12,431	18.2
Unknown	1	0.1	10	<0.1

[a] BCC, basal cell carcinoma.
[b] Restricted to respondents to first survey (baseline) questionnaire who were cancer free at baseline.
[c] As of the time subjects responded to the first questionnaire (1983–1989).
[d] Subjects were placed in the "highest" educational category applicable, with college ranked after radiological training, which was ranked after high school education.

Risk for BCC rose with increasing alcohol intake among the combined group of men and women (P for trend = 0.001), although risk dropped in the highest consumption category (Table 2). Comparable relationships were found among men and women. Results were also similar when analyses were restricted to the subset of cases for whom the BCC diagnosis was validated by medical records and when trends were assessed by use of the median value for each category of intake.

In the combined group of men and women, a slight excess risk of BCC was found among former smokers, whereas no increased risks were observed among current smokers (Table 2). Among women, risk of BCC was neither related to intensity of smoking (packs/day) nor to duration of smoking. Among men, however, BCC risk decreased significantly with longer duration of smoking, although risk was significantly elevated among those in the highest smoking intensity category (>2 packs/day). In neither men nor women was the number of cigarette pack-years related to risk.

Discussion

We found the expected elevated associations between BCC and increasing age, fair skin tone, lighter eye and hair color, and

Table 2 Multivariate[a] relative risk of basal cell carcinoma with 95% confidence interval by categories of alcohol intake and smoking

Characteristics	Men (n = 324)			Women (n = 1,036)			Combined men and women (n = 1,360 cases; 67,011 noncases)		
	No. of cases	RR[b]	95% CI	No. of cases	RR	95% CI	No. of cases/ noncases	RR	95% CI
Alcohol intake (drinks/week)									
0	52	1.0		181	1.0		233/11,546	1.0	
<1–2	148	1.4	1.0–2.0	550	1.0	0.8–1.2	698/38,189	1.1	0.9–1.3
3–6	55	1.4	1.0–2.1	173	1.2	1.0–1.5	228/9,856	1.3	1.1–1.5
7–14	53	1.7	1.1–2.5	115	1.3	1.0–1.7	168/5,816	1.4	1.2–1.7
>14	13	1.2	0.7–2.3	11	0.9	0.5–1.7	24/1,166	1.0	0.7–1.6
P for trend			0.08			0.01			0.001
Overall smoking status									
Never smoker	112	1.0		491	1.0		603/32,717	1.0	
Former smoker	150	1.2	0.9–1.5	308	1.1	0.9–1.3	458/18,259	1.1	1.0–1.3
Current smoker	56	0.7	0.5–1.0	231	1.0	0.8–1.1	287/15,463	0.9	0.8–1.0
Packs/day									
Never smoker	112	1.0		491	1.0		603/32,717	1.0	
<0.5	48	1.1	0.8–1.6	167	1.0	0.8–1.2	215/10,535	1.0	0.9–1.2
0.5–1	74	0.9	0.7–1.2	230	1.0	0.9–1.2	304/14,089	1.0	0.9–1.2
>1–2	65	0.9	0.7–1.2	131	1.1	0.9–1.3	196/8,365	1.0	0.9–1.2
>2	21	1.7	1.0–2.7	10	1.0	0.5–1.9	31/811	1.5	1.0–2.1
P for trend			0.83			0.54			0.31
Smoking duration (yrs)									
Never smoker	112	1.0		491	1.0		603/32,717	1.0	
<10	47	1.3	0.9–1.9	146	1.1	0.9–1.3	193/9,773	1.2	1.0–1.4
10–19	73	1.2	0.9–1.6	203	1.1	0.9–1.3	276/13,723	1.1	1.0–1.3
20–29	44	0.8	0.5–1.1	112	0.9	0.7–1.1	156/6,921	0.9	0.7–1.0
30+	42	0.7	0.5–1.1	72	1.0	0.7–1.3	114/3,029	0.9	0.7–1.1
P for trend			0.03			0.45			0.17
Pack-years									
Never smoker	112	1.0		491	1.0		603/32,717	1.0	
<10	79	1.2	0.9–1.6	267	1.1	0.9–1.2	346/17,017	1.1	1.0–1.3
10–29	64	0.8	0.6–1.1	179	1.0	0.8–1.2	243/11,680	1.0	0.8–1.1
30+	62	1.0	0.7–1.3	85	1.0	0.8–1.3	147/4,469	1.1	0.9–1.3
P for trend			0.91			0.95			0.65

[a] Relative risk estimated using Cox proportional hazards regression analysis with age as the time scale, stratifying at baseline on birth cohort in 5-year intervals. Adjusted for years smoked (never smoker, ≤9, 10–19, 20–29, ≥30 years) in the case of alcohol analysis; alcohol consumption (0, <1–2, 3–6, 7–14, >14 drinks/week) in the case of the smoking analysis; in all analyses skin pigmentation (fair, medium/dark), hair color (red/auburn, blonde, light brown, dark brown/black), race (white, nonwhite, unknown), education (high school, radiation technology program, ≥1 years of college/graduate school, other education), body mass index (quartiles), decade began work as a radiation technologist, and proxy measures for residential childhood and adult sunlight exposure (quintiles). Missing information for the characteristics was analyzed with separate dummy variables.

[b] RR, relative risk; CI, confidence interval.

surrogates for residential sun exposure (2, 5, 13–15) among a large cohort of United States radiological technologists. We found no clear association between BCC and cigarette smoking, which is consistent with the male Health Professionals Follow-up Study (14) the female Nurses Health Study (13), and others (7, 8, 15). The decreasing risks that we observed with increasing duration of smoking were limited to men, but were seemingly inconsistent with the increased risk that we found for men who smoked more than two packs/day. In contrast, Karagas *et al.* (16) found that BCC was inversely associated with heavy smoking, although not with smoking for a long duration. In addition, De Hertog *et al.* (17) found an inverse association with smoking limited to one type of BCC, superficial multifocal basal cell carcinoma. Possibly these findings of reduced risk of BCC with smoking may be an artifact of multiple comparisons. However, the number of inverse findings with smoking, even taking into account apparent inconsistencies in the patterns of risk, argues for further follow-up in a study with greater histological precision and more detailed assessment of smoking factors and potential confounders.

Our findings of increasing risks for BCC with increasing alcohol intake among men and women are similar to those reported by Fung *et al.* (6), although we could not analyze risk by type of alcohol beverage (*i.e.*, beer or wine) consumed. Although Fung *et al.* observed a significant positive trend, risk was not monotonically increased in either the male Health Professionals or the female Nurses cohorts. Specifically, risks rose to a significant 29% excess associated with drinking 15.0–29.9 g/day and then decreased to an excess risk of only 12% for the highest intake category, ≥30 g/day. In comparison, the increased risk among USRT subjects rose to ~40% and then disappeared among those in the highest intake group, in roughly comparable categories. However, the highest category of intake among USRT subjects contained relatively few subjects (n = 24), reducing the precision of the point estimate. Even so, the only two large prospective studies of BCC and alcohol intake report very similar results. As noted earlier, previous case–control studies did not observe an association with alcohol consumption, but Kune *et al.* (7), with 53 cases, and Sahl *et al.* (8), with only 49 cases, may not have had sufficient power to detect modest effects.

Alcohol is a known risk factor for several cancer sites, including oral and pharyngeal, esophageal, laryngeal, liver and breast cancer (18–21). The role of alcoholic beverages in the causal pathway, however, remains unclear. Clinical observations and laboratory findings suggest that alcohol intake may

have a negative impact on the immune system, contribute to the formation of DNA adducts that interfere with normal DNA function, and induce excessive cell proliferation, among other effects (21).

The nonmonotonic relationship between BCC and alcoholic beverages observed in our study as well as that of Fung *et al.* (6) is puzzling. Fung *et al.* speculate that this particular risk pattern, as well as the differential relationship with various types of alcohol consumed, suggest that factors other than the alcoholic content of the beverages or possibly uncontrolled confounders may account for the risk pattern. In the future it would be valuable to estimate the individual sun exposure of the participants, because time outdoors may have contributed to the increasing risk or limited outdoor time may possibly help explain the unexpectedly low risk of those in the highest consumption category. It is also possible that individuals with the highest alcoholic intake disproportionately consume particular beverages not associated with risk, such as beer, which Fung *et al.* (6) found was not related to BCC.

There are several limitations to the present study, including the lack of information on sun exposure, certain host susceptibility factors (*e.g.*, propensity to burn), types of alcoholic drinks consumed, and changing drinking patterns over time, as well as incomplete case validation. Advantages include the large number of BCC cases with a nationwide geographical distribution, the prospective collection of information on major risk factors, and the availability of information on certain major potential confounders, including constitutional and lifestyle factors. Future studies examining a potential association with alcohol intake should refine exposure and covariate information, including types of alcohol consumed, changes in patterns of consumption, and lifetime sun exposure.

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